DISSEMINATED VIRAL INFECTIONS

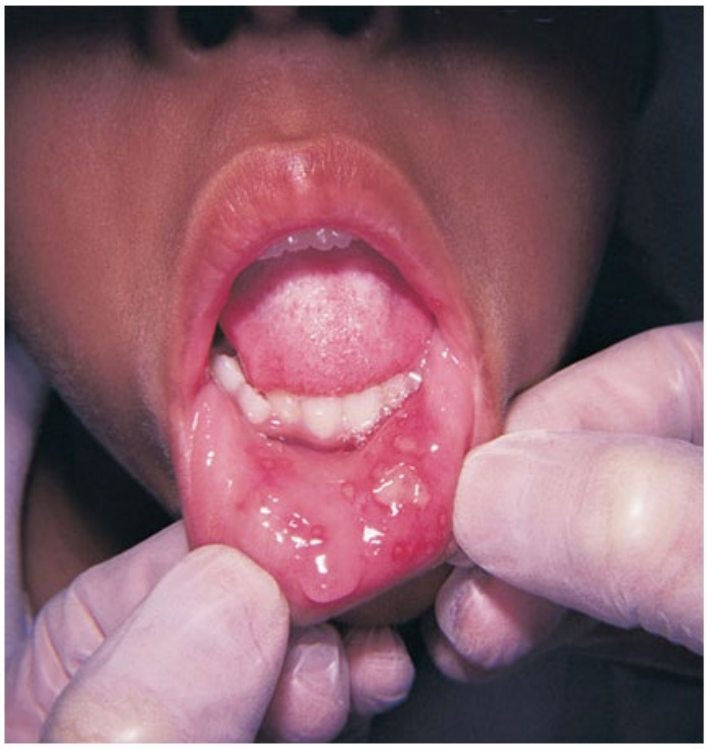
VIRAL INFECTIONS ARE AMONG THE MOST COMMON ILLNESSES ENCOUNTERED IN EMERGENCY. ALTHOUGH THE MAJORITY ARE TRIVIAL, THERE ARE CERTAIN INFECTIONS THAT MAY BE LIFE-THREATENING

HERPESVIRUSES:

- A class of enveloped DNA viruses that cause a wide variety of human illnesses
- May result from primary infection or reactivation of latent infection
- The most serious illness is found in immunocompromised individuals

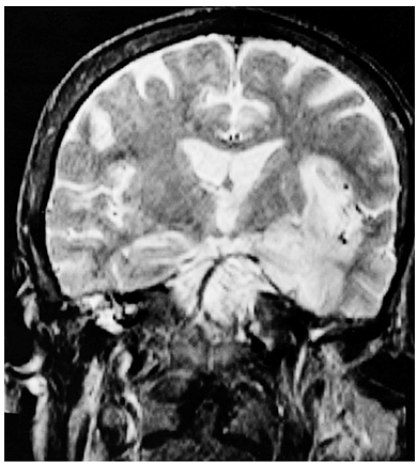
HSV 1 AND 2 INFECTIONS:

- Closely related viruses that commonly cause oral and genital ulcers → rarely causes devastating CNS disease
- Treatable with antiviral drugs, so early recognition of serious illness is important
- EPIDEMIOLOGY:
    - HSV-1 usually acquired during childhood through nonsexual contact
    - HSV-2 almost always sexually transmitted
    - HSV-1 is one of the most common causes of viral encephalitis → occurs in those <20 and >50
        - Mortality for untreated encephalitis is ~70%
        - Neonates with HSV have high frequency of both visceral and CNS involvement → risk is highest when the mother acquires the infection in the third trimester
- PATHOPHYSIOLOGY:
    - HSV are transmitted via exchange of saliva, vesicular fluid, semen and cervical fluid → the virus must come into contact with abraded skin or mucosal surfaces, where it replicates before becoming latent in sensory ganglia
        - Reactivated virus travels to cutaneous surface and leads to vesicular eruptions
    - The virus is though to gain access to the brain by the olfactory or trigeminal nerves with a PREDILECTION FOR THE MEDIAL AND INFERIOR TEMPORAL LOBES
    - Multi-organ disease is much more common in the immunosuppressed and neonates
- CLINICAL FEATURES:
    - Symptoms depend on anatomic site involved, immune status of the host and whether the infection is primary or recurrent
    - Gingivostomatitis and pharyngitis are typical manifestations of primary HSV-1, whereas recurrence manifests as orolabial lesions



Primary herpetic gingivostomatitis

- Herpetic keratitis can result in corneal blindness
- HSV-1 and 2 can cause identical genital lesions, but genital lesions are much more common with HSV-2
- THE HALLMARK OF HSV ENCEPHALITIS IS ACUTE ONSET OF FEVER AND NEUROLOGICAL SYMPTOMS (hemiparesis, cranial nerve anomalies, ataxia, focal seizures, altered mental state, behavioural anomalies)
- HSV infection in immunocompromised hosts can lead to widespread dissemination with multi-organ involvement
    - Organ transplant patients may develop oesophagitis, hepatitis, colitis, pneumonia
    - Severely burned patients are also prone to life-threatening herpetic infection
- DIAGNOSIS:
    - Specimen for viral culture can be obtained from fluid of an unroofed vesicle
    - Identification of temporal lobe lesions on CT or MRI is strongly suggestive of HSV encephalitis
    - CSF analysis shows lymphocytic pleocytosis inmost cases with PCR testing being the modality of choice for HSV meningoencephalitis (94% sensitive and 98% specific)



- TREATMENT:
  - Depends on severity of the disease
  - ACICLOVIR is the drug of choice in patients with HSV encephalitis or disseminated disease and in immunocompromised patients with severe mucocutaneous disease

For adults and children in suspected or proven cases, use:

aciclovir 10 mg/kg IV, 8-hourly for at least 14 days (adjust dose for renal function, see Table 2.31).

For full-term neonates, use:

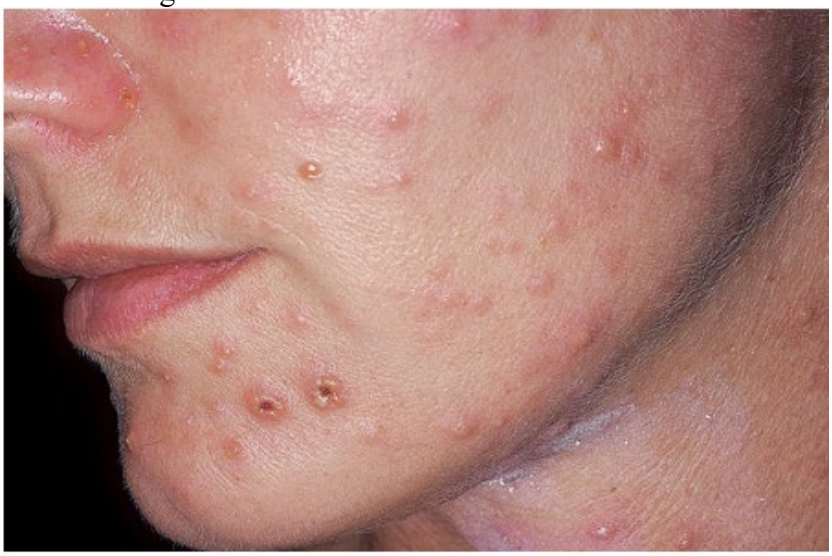
aciclovir 20 mg/kg IV, 8-hourly for 21 days (adjust dose for renal function).

  - Even with early treatment, patients with HSV encephalitis have high mortality, if left untreated, MORTALITY IS 70%
    - Survivors are often left with neurologic sequelae
  - Predictors of poor outcome:
    - GCS <6
    - Focal CNS lesions on CT
    - Increased age
    - Start of antivirals >4 days post-onset
  - CONSIDER ADDING ACICLOVIR TO STANDARD ANTIBIOTIC THERAPY IN PATIENTS IN WHOM DIAGNOSIS OF ACUTE BACTERIAL MENINGITIS IS BEING CONSIDERED

VARICELLA AND HERPES ZOSTER:

- VZV is the causative organism of both chickenpox (varicella) and herpes zoster (Shingles). It is extremely contagious, usually acquired in childhood
- EPIDEMIOLOGY:
  - Chickenpox occurs year round, with infection rates ranging from 60-100% in exposed individuals
  - Herpes Zoster can occur once an immune response against the virus wanes → usually with advancing age
    - 90% of adults show serologic evidence of VZV and the lifetime incidence is ~10-20%

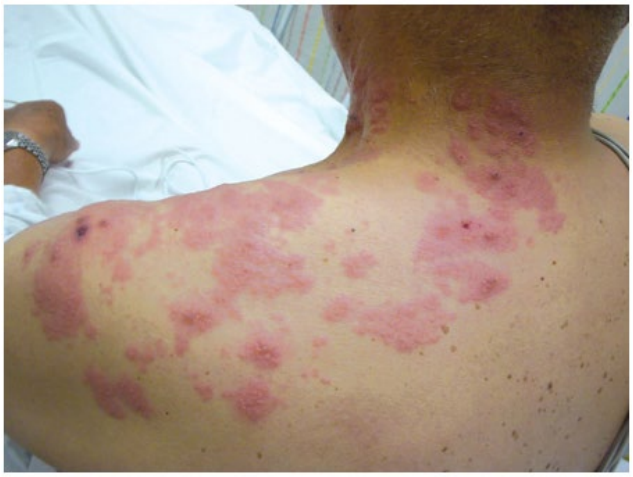
        - Iatrogenic immune suppression, HIV, organ transplantation, lymphoproliferative disorders predispose to Herpes Zoster
- PATHOPHYSIOLOGY:
    - VZV spreads to the respiratory mucosa of a susceptible host via aerosolised droplets, but can also be spread by direct contact (not as highly contagious by this method)
    - Virus multiples in regional lymph nodes and then disseminates → it is contagious until all the lesions have crusted over
    - VZV remains latent in the DRG and can later reactivate along dermatomes (Shingles)
- CLINICAL FEATURES:
    - VARICELLA:
        - A febrile illness with a vesicular rash
        - Rash is superficial and appears in crops, with lesions of varying stages



        - Bacterial superinfection of the skin can cause serious illness
        - Other serious complications are seen in the immunocompromised, and those at extremes of age
        - Children with lypmhoma or leukaemia may develop progressive varicella in which vesicles continue to erupt in the second week of the illness sometimes with visceral involvement of the lung, liver and brain
            - CNS complications include cerebellar ataxia, meningitis, encephalitis
            - Pneumonitis ca be severe and is more common in pregnant women

    - HERPES ZOSTER:
        - Begins with prodromal phase of pain, itching and paraesthesiae in one or more dermatomes
        - Followed by development of the rash

- Eruption DOES NOT CROSS MIDLINE
- Most commonly affects the chest, but can appear at any dermatomal level
- Herpes zoster ophthalmicus can cause blindness and is the result of reactivation along V1
- If it involves facial nerve → RAMSAY HUNT SYNDROME, lesions along auditory canal with facial paralysis
- Herpes zoster along ≥3 dermatomes is a clue to immunodeficiency



- TREATMENT:
  - VARICELLA:
    - Most healthy patients need only supportive care for chickenpox
    - Consider acyclovir for those at risk of complications (age >12, patients with chronic skin (e.g. atopic dermatitis) or pulmonary disorders, long-term salicylate, immunocompromised)

In **pregnant women** with varicella, oral aciclovir for 7 to 14 days is recommended if commenced within 72 hours of the onset of the rash; see below for dosing and seek expert advice.

In **immunocompromised patients with severe disease** and in **normal patients with complications** of varicella (eg pneumonitis, encephalitis or hepatitis), irrespective of the duration of the rash, use initially:

aciclovir (adult and child) 10 mg/kg IV, 8-hourly (adjust dose for renal function, see Table 2.31).

When clinically improved, switch to oral therapy to complete a minimum of 10 days of therapy. Use:

1 **famciclovir 250 mg orally, 8-hourly**
or famciclovir 500 mg orally, 8-hourly (in immunocompromised patients)

OR

1 **valaciclovir 1 g orally, 8-hourly**

OR

2 **aciclovir 800 mg (child: 20 mg/kg up to 800 mg) orally, 5 times daily (aciclovir is preferred in children and in pregnancy; seek expert advice).**

For **immunocompromised patients with less severe disease**, irrespective of the duration of the rash, use oral therapy as above to complete 7 to 14 days of therapy.

Varicella in the nonimmune can be modified or prevented following exposure to an infected patient either by the use of varicella vaccine given within 5 days of exposure or by the administration within 96 hours of exposure of high-titre varicella-zoster immunoglobulin (ZIG). The latter product is available on a restricted basis from the Australian Red Cross Blood Service for the prevention of varicella in high-risk nonimmune, such as the immunocompromised and pregnant women who are close to term. See the *Australian Immunisation Handbook* [URL] for a detailed outline of postexposure management.

- Note last paragraph above in terms of use of immunoglobulin to avoid complications of varicella (has to be used within 96 hours of exposure)
- TREATMENT OF HERPES ZOSTER:
    - Primary goal in treatment of herpes zoster is to reduce severity of post-herpetic neuralgia
    - Using antiviral therapy in immunocompromised may reduce risk of severe, disseminated disease → start antivirals within 72 hours of onset of rash and consider treatment >72 hours if new vesicles are still present or developing
    - Zoster ophthalmicus requires valaciclovir and ophthalmological assessment urgently
    - NARCOTIC ANALGESIA SOMETIMES NECESSARY

Antiviral treatment should be used in any patient seen within 72 hours of the onset of vesicles, all patients with ophthalmic herpes zoster, and in immunocompromised patients. Use:

1 **famciclovir 250 mg orally, 8-hourly for 7 days**
or famciclovir 500 mg orally, 8-hourly for 10 days (in immunocompromised patients)

OR

1 **valaciclovir 1 g orally, 8-hourly for 7 days**

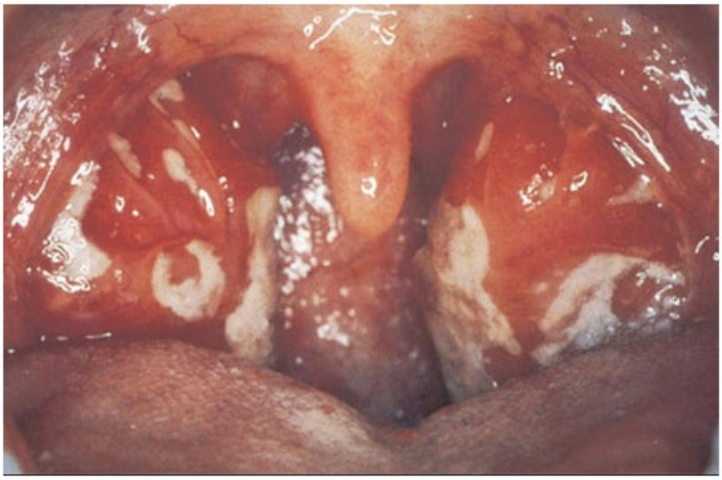
OR

2 **aciclovir 800 mg (child: 20 mg/kg up to 800 mg) orally, 5 times daily for 7 days**
(aciclovir is preferred in children and in pregnancy, seek expert advice).

- PREVENTION:
    - Vaccines are available to prevent both chickenpox and herpes zoster, although neither vaccine is 100% effective
    - Use of IVIG is usually limited to nonimmune pregnant women and the severely immunosuppressed

EPSTEIN-BARR VIRUS INFECTION:

- EBV is implicated in a variety of human illnesses:
    - Infectious mononucleosis
    - Cancers → B-cell lymphoma, Hodgkin disease, Burkitt lymphoma, nasopharyngeal carcinoma
- Two age-related peaks → early childhood and young adulthood
- Requires close contact for transmission
- PATHOPHYSIOLOGY:
    - Transmitted via salivary secretions (the “Kissing disease”)
    - Disseminates through the bloodstream
    - Virus then infects B-LYMPHOCYTES and cases an increase in T-lymphcytes with resultant enlargement of lymph node tissue
    - In immunocompromised individuals with decreased T-cell function, B cells continue to proliferate with potential neoplastic transformation
- CLINICAL FEATURES:
    - Manifestations depend on age and immune status
    - IM presents as fever, lymphadenopathy and pharyngitis (often with extensive tonsillar exudates)



- Patients treated with ampicillin or amoxicillin for suspected GABHS pharyngitis often develop a rash if they have EBV infection
- EBV can affect nearly all organ systems → Guillain-Barre syndrome has been described, as well as meningoencephalitis, hepatitis, myocarditis, haematologic disorders
    - RARELY, death can result from splenic rupture, CNS complication or airway obstruction
- DIAGNOSIS:
    - History, exam plus FBC and monospot test can provide confirmation → typically there is a lymphocytosis with >50% lymphocytes
    - MONOSPOT test → identifies heterophile antibodies that agglutinate animal erythrocytes and a positive result is considered diagnostic of EBV infection in the right setting → can be negative early
- TREATMENT → rest, analgesia and adequate hydration are the mainstays of treatment
    - Advise patients to avoid contact sport for minimum four weeks to avoid splenic injury

CYTOMEGALOVIRUS INFECTION:

- Causes wide variety of disease, ranging from asymptomatic (most cases) to life-threatening pneumonia in transplant patients
- Causes a primary infection then recedes into lifelong latency unless the patient becomes severely immunosuppressed
- EPIDEMIOLOGY:
    - CMV is not thought to be highly contagious, transmission requires repeated or prolonged exposure
    - Virus is spread by sexual contact, saliva, breastfeeding and transplantation as well as trasnplacentally and through blood transfusion
    - Highest risk for transplant patients who are seronegative and then acquire a CMV-positive organ
- CLINICAL FEATURES:

- Primary infection in healthy individuals is usually asymptomatic although can cause IM-like illness with prolonged fever,myalgias, lymphocytosis but no pharyngitis
- Severe disease in the otherwise healthy host most commonly results in hepatitis, colitis, Guillain-Barre syndrome, encephalitis and haemolytic anaemia
- Congenital and neonatal infections are associated with some of the most important complications of primary CMV infection
  - Hepatosplenomegaly
  - Jaundice
  - Microcephaly
  - Petechiae
  - Growth retardation
    - Severe infections carry a high mortality and those who survive often have neurologic sequelae
- Infections in immunocompromised patients can be severe and involve any organ (can be result of reactivation from latent virus)
  - In transplant patients, the disease typically begins in the transplanted organ → then disseminates to cause pneumonia, hepatitis and CNS involvement
  - Begins as prolonged fever, night sweats and fatigue
  - In HIV patients with CD4 counts <50 → retinitis is the most common manifestation

- DIAGNOSIS:
  - Specific diagnosis is NOT MADE IN EMERGENCY
  - Body fluids can be sent for antigen testing, PCR, antibody testing, histologic analysis and viral culture
- TREATMENT:
  - Several systemic antiviral agents are active against CMV → ganciclovir, valganciclovir, foscarnet and cidofovir
  - Transplant patients are treated more aggressively and can include CMV hyperimmune globulin along with antiviral therapy

The cornerstone of therapy remains ganciclovir, which is given intravenously due to poor bioavailability. The oral prodrug valganciclovir may be used to treat infection in mild to moderate disease, or as step-down therapy once a response to intravenous treatment has been established. Use:

1 **ganciclovir 5 mg/kg IV, 12-hourly for 14 days**

OR

1 **valganciclovir 900 mg orally, 12-hourly for 14 days.**

Treatment may need to be extended if CMV viraemia persists, due to risk of relapse. Accordingly, treatment should be monitored with regular CMV viral load to ensure response.

Ganciclovir resistance may occur and is manifested by a rise in CMV viral load, with or without a recurrence of symptoms. This should be correlated with resistance testing where available. If ganciclovir resistance is confirmed, or if ganciclovir is contraindicated, use:

foscarnet 90 mg/kg IV, 12-hourly for 14 days.